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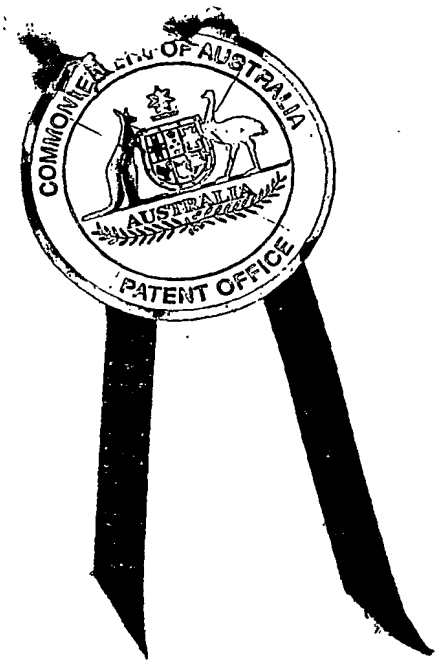
I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003905858 for a patent by IMMUNAID PTY LTD as filed on 24 October 2003.

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J. Billingsley

JULIE BILLINGSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES

# AUSTRALIA

# Patents Act 1990

**ImmunAid Pty Ltd**

**PROVISIONAL SPECIFICATION**

*Invention Title:*

*Method of Therapy*

The invention is described in the following statement:

# METHOD OF THERAPY

## FIELD OF THE INVENTION

Numerous diseases have been linked to the production of regulator cells. The present invention relates to the observation that regulator cells are cycling in these diseases. Based on these observations, the present invention provides methods for treating diseases such as cancer and a HIV infection. The present invention also relates to methods of determining when therapy should be administered to a patient.

## BACKGROUND OF THE INVENTION

In the past, attempts have been made to trigger the immune system to mount an efficient response against malignant cells. Despite significant and promising progress, such a response has yet to be fully attained and many immune based therapies have proved disappointing.

Numerous studies using *in vitro* cellular assays demonstrate that cytotoxic lymphocytes have the ability to kill tumour cells. Why this immune based destruction does not effectively control tumour growth *in vivo* is a conundrum. The cancer patient also has increased concentration of circulating immune complexes, indicating the immune system is active, particularly against certain tumour antigens. The level of these immune complexes can increase with disease progression (Horvath *et al*, 1982; Aziz *et al*, 1998).

Regulatory cells (also referred to in the art as suppressor cells) have been implicated in a subjects' immune response to cancer (North and Awwad, 1990; WO 03/068257). As most cancer antigens are actually produced by the patient they are considered as "self" by the immune system. Upon the presence, and/or increased quantity, of tumour antigen the host's immune system mounts a response characterized by the production of effector cells which target cells producing the tumour antigen. However, in many instances these effector cells are recognized by the immune system as targeting the hosts own cells, and hence a population of regulator cells are produced to ablate the effector cell population. Thus, the production of these regulator cells limits the ability of the immune system to effectively remove cancer cells.

More recently, regulator cells have been shown to be involved in a subjects' immune response to a viral infection. WO 02/13828 describes the production of regulator cells during retroviral infection, and methods of treating such infections by ablating the regulator cell population whilst maintaining the effector cell population. Furthermore, Peterson *et al* (2002) observed that a population of CD4+ regulator cells

were suppressing the ability of CD8+ effector cells to control Friend murine retrovirus infections in mice.

Measurements of certain acute-phase protein plasma concentrations can be of diagnostic or prognostic value under specific clinical conditions. The best known acute-phase protein is C-reactive protein (CRP). CRP is a plasma protein that rises in the blood with the inflammation from certain conditions. The level of CRP in blood plasma can rise as high as 1000-fold with inflammation. Conditions that commonly lead to marked changes in CRP include bacterial and viral infection, trauma, surgery, burns, inflammatory conditions, coronary and vascular disease and advanced cancer.

Most acute phase proteins are synthesized by hepatocytes, some are produced by other cell types, including monocytes, endothelial cells, fibroblasts and adipocytes. Acute phase proteins include serum amyloid A (SAA), CRP and serum amyloid P component (SAP).

The immediate responsiveness of CRP and SAA to stimuli, together with their wide concentration range and ease of automated measurement, have led to plasma CRP and SAA levels being used to monitor accurately the severity of inflammation and the efficacy of disease management during certain disease conditions.

WO 03/070270 describes the use of acute phase inflammatory markers in regimes for the effective treatment of HIV. These methods rely on at least partially "resetting" the immune system by a treatment such as HAART followed by the analysis of acute phase inflammatory proteins as markers for effector/regulator cell expansion. The emergence of acute phase inflammatory proteins is linked to effector cell expansion, which occurs before regulator cell expansion, and thus the patient can be treated with a suitable agent which allows the effector cell population to be maintained whilst destroying, or preventing the production of, regulator cells. In essence, upon withdrawal of HAART treatment it was considered that the patient's immune system would treat the re-emerging HIV particles as a new infection, and hence a new population of effector cells would be produced.

Similar to WO 03/070270, WO 03/068257 relates to at least partially resetting the immune system, however, in this instance in the context of the treatment of cancer. Again, the treatment is focussed on the initial re-emergence of effector cells following a reduction in tumour load through techniques such as surgery or the administration of anti-proliferative drugs.

Neither WO 02/13828, WO 03/070270 or WO 03/068257 appreciate that the immune response, including regulator cell populations, are cycling in a cancer or HIV patient regardless of the administration of treatment for these diseases. The present

invention is based on the realization of this cycling, and thus provides methods for the treatment of diseases linked to regulator cell production.

## SUMMARY OF THE INVENTION

The present inventor has surprisingly found that both effector cell and regulator cell numbers cycle during disease states characterized by the presence of regulator cells. This cycling occurs on a regular basis of approximately 14 to 15 days in humans, with effector cell expansion against a target antigen being followed by the expansion of regulator cells directed against the effectors. Upon control of the effector cells by the regulator cells the numbers of both types of cells decrease, which in turn is followed by the same cycle due to the continuous presence or incomplete removal of antigen which results in an oscillating, persistent but ineffective immune response against the, for example, tumour or virus.

Knowledge of this cycle can be used to treat diseases where it is known that the emergence of regulator cells is detrimental to the patient. Examples of such diseases include cancer and persistent infections such as by the human immunodeficiency virus. More specifically, treatment of a patient can be timed such that effector cell numbers against an a cellular or viral antigen are maximized whilst regulator cell numbers are reduced or abolished.

In fact, the present inventor has noted that the treatment of a variety of cancers with anti-proliferative drugs results, on average, in a complete response rate in the range of 6.5 to 7%. This range of 6.5 to 7% is consistent with an about 14 to 15 day cycle of effector cell expansion followed by regulator cell expansion. More specifically, when not taking into consideration the cycling of effector and regulator cells, a medical practitioner has an approximate 1 in 14.5 chance (6.8%) of administering an anti-proliferative drug at a time where effector cells numbers are high but regulator cell numbers have only begun to expand and hence are vulnerable to treatments which target dividing cells. This leaves high numbers of effector cells which target the cancer cells, resulting in a complete response to the therapy.

Accordingly, in a first aspect, the present invention provides a method for determining when an agent which inhibits the production of, limits the function of, and/or destroys, regulator cells, should be administered to a patient suffering from a disease characterized by the production of regulator cells, the method comprising monitoring the patient, or samples obtained therefrom, for any one of a) effector cell numbers or activity, b) regulator cell numbers or activity, or c) a marker of a) or b).

In a further aspect the present invention provides a method of treating a disease characterized by the production of regulator cells, the method comprising;

i) monitoring a patient for any one of:

a) an increase in the number or activity of regulator cells,

b) an increase in the number or activity of effector cells,

c) an increase or decrease in a marker for a) or b), and

ii) exposing the patient to an agent which inhibits the production of, limits the function of, and/or destroys, regulator cells,

wherein the timing of administration is selected such that the activity of effector cells is not significantly reduced.

Preferably, the disease characterized by the production of regulator cells is selected from, but not limited to, cancer and an infection.

The infection can be caused by any type of infectious agent such as, but not limited to, a virus, bacteria, protozoa, nematode or fungus. Preferably, the infectious agent causes chronic persistent infection characterized by the patient immune system not being able to eliminate the infectious agent. Examples of infectious agents which cause chronic persistent infection are viruses such as HIV, the hepatitis B virus and the hepatitis C virus.

As antigen load, for example from increased tumour growth or viral replication, increases following regulator cell activity the patients' immune system responds in a manner similar to a first time exposure to the antigen. This immune response includes the production of acute phase inflammatory markers such as serum amyloid A and c-reactive protein. An appropriate time to administer the agent (which limits the function of, and/or destroys, regulator cells) is between when the levels of acute phase inflammatory marker have peaked and before these markers begin to rise in the next cycle. Accordingly, a particularly preferred marker is an acute phase inflammatory marker. More preferably, the acute phase inflammatory marker is selected from, but not limited to, the group consisting of serum amyloid A, serum amyloid P and c-reactive protein.

In one embodiment, the patient is monitored for an increase in the number or activity of regulator cells by the analysis of CD4+CD8- T cell levels. With regard to this embodiment, it is preferred that the agent is administered as soon as CD4+CD8- T cells are detected.

In another embodiment, the patient is monitored for an increase in the number or activity of effector cells by the analysis of CD8+CD4- T cell levels. With regard to this

embodiment, it is preferred that the agent is administered approximately when CD8+CD4- T cell numbers have peaked.

In a further embodiment, the disease is cancer and the patient is monitored for fluctuations in the levels of tumour antigen(s). With regard to this embodiment, it is preferred that the agent is administered approximately when levels of tumour antigen begins to decrease.

In a further embodiment, the disease is caused by an infectious agent and the patient is monitored for fluctuations in the levels of antigen(s) produced by the infectious agent. With regard to this embodiment, it is preferred that the agent is administered approximately when levels of antigen, or infectious organisms or viruses (viral load), begins to decrease.

Typically, the patient will need to be monitored for a sufficient length of time to ensure that the dynamics of effector cell and regulator cell cycling within the patient is understood. In particular, individual variation may be encountered with regard to, for example, i) the length of the cycle, ii) the absolute numbers of effector or regulator cells during the cycle, or iii) the levels of acute phase inflammatory markers during the cycle. Such variation may be exaggerated in patients with advanced cancer or infection, where the patients immune system has been compromised for a considerable length of time.

A further complicating factor will be if the patient has recently acquired a disease or trauma unrelated to that being treated. For example, a patient being treated for a HIV infection may also contract the common flu virus. The presence of the flu virus will result in, for example, an increase in acute phase inflammatory markers independent of the cycling of these markers which is occurring due to the HIV infection. Other diseases which may cause complications in monitoring effector/regulator cell cycling for use in the methods of the present invention include, rheumatoid arthritis, ulcers and chronic gum disease. Accordingly, it is desirable to monitor the patient for any factors which may result in elevated levels of, for example, acute phase inflammatory markers to ensure that the factor being monitored truly reflects effector/regulator cell cycling resulting from the disease being treated.

Preferably, the patient is monitored for a period of at least 7 days, more preferably at least 14 days, more preferably 21 days, and even more preferably at least 28 days.

Furthermore, it is preferred that the patient is monitored as frequently as possible to ensure effector/regulator cell cycling within a given patient is suitably characterized. Naturally this will ensure that the agent is administered at the

appropriate time and that any small variations in effector/regulator cell numbers or activity, or markers thereof, is not misinterpreted. Preferably, the patient is monitored at least every 3 days, more preferably at least every 2 days, and most preferably at least every day. Monitoring may occur more frequently, for instance every 12 hours, when the cycling is reaching a stage where it is likely that the timing would be appropriate to administer the agent.

Preferably, the agent is selected from the group consisting of anti-proliferative drugs, radiation, and antibodies which inhibit the down regulation activity of the regulator cells. Preferably, the anti-proliferative drug is selected from the group consisting of, but not limited to, taxol, vincristine, vinblastine and anhydro vinblastine.

Examples of preferred antibodies include, but are not limited to, anti-CD4+, anti-CTLA-4 (cytotoxic lymphocyte-associated antigen-4), anti-GITR (glucocorticoid-induced tumour necrosis factor receptor), anti-CD28 and anti-CD25.

The present invention also provides for the use of an assay which detects a marker of effector cell numbers or activity for determining when an agent which inhibits the production of, limits the function of, and/or destroys, regulator cells is administered to a patient suffering from a disease characterized by the production of regulator cells.

Preferably, the marker is an acute phase inflammatory marker. More preferably, the marker is a positive acute phase inflammatory marker. Even more preferably, the marker is selected from the group consisting of, but not limited to, serum amyloid A and c-reactive protein.

The present invention also provides for the use of an assay which detects effector cell numbers or activity for determining when an agent which inhibits the production of, limits the function of, and/or destroys, regulator cells is administered to a patient suffering from a disease characterized by the production of regulator cells.

Preferably, the assay detects the number of CD8+CD4- T cells in the patient, or sample obtained therefrom.

Furthermore, the present invention also provides for the use of an assay which detects regulator cell numbers or activity for determining when an agent which inhibits the production of, limits the function of, and/or destroys, regulator cells is administered to a patient suffering from a disease characterized by the production of regulator cells.

Preferably, the assay detects the number of CD4+CD8- T cells in the patient, or sample obtained therefrom.

In a further aspect, the present invention provides for the use of an agent which inhibits the production of, limits the function of, and/or destroys, regulator cells for the

manufacture of a medicament for administering to a patient suffering from a disease characterized by the production of regulator cells, wherein the agent is administered at a time selected such that the activity of effector cells is not significantly reduced, and wherein the patient has not been exposed to a treatment for the disease for at least 14 days.

Preferably, patient has not been exposed to a treatment for the disease for at least 21 days, more preferably at least 28 days.

As would be readily appreciated by those skilled in the art, the methods of the present invention may be repeated to provide a more complete treatment.

Preferably, the subject/patient is a mammal. More preferably, the mammal is a human.

As will be apparent, preferred features and characteristics of one aspect of the invention are applicable to many other aspects of the invention.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

The invention is hereinafter described by way of the following non-limiting Examples and with reference to the accompanying figures.

## BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

Figure 1. A) C-reactive protein and tumour marker CA125 levels over a 14 day period in a patient with ovarian cancer. B) Serum amyloid A levels in the same patient over the same period (C-reactive protein levels from A) duplicated).

Figure 2. C-reactive protein levels in response to taking a first human HIV patient off HAART treatment.

Figure 3. Viral load and CRP fluctuations in a second HIV patient following the completion of HAART.

## DETAILED DESCRIPTION OF THE INVENTION

### Definitions

As used herein the terms "treating", "treat" or "treatment" include administering a therapeutically effective amount of an agent sufficient to reduce or eliminate at least one symptom of the disease.

As used herein, the term "tumour load" generally refers to the number of cancerous cells in a subject at any given time. Measuring the level of tumor antigen in the subject can be considered as an indication of tumour load.

As used herein, the term "viral load" generally refers to the number of viral particles in a subject at any given time. Measuring the level of viral antigen in the subject can be considered as an indication of viral load.

"Regulator cells" include, but are not necessarily limited to, a subpopulation of CD4+ T cells. Such cells may also be referred to in the art as "suppressor cells". Regulator cells may either act directly on effector cells or may assert their affects upon effector cells through other mechanisms.

CD4+ cells express the marker known in the art as CD4. Typically, the term "CD4+ T cells" as used herein does not refer to cells which also express CD8. However, this term can include T cells which also express other antigenic markers such as CD25.

"Effector cells" include, but are not necessarily limited to, the T cell population known as CD8+ cells.

As used herein, the term "limits the function of, and/or destroys" when referring to the exposure of the "regulator cells" to the agent means that the number, and/or activity, of regulator cells is down-regulated by the agent. Most preferably, the number, and/or activity, of regulator cells is completely eradicated by the agent.

As used herein the term "disease characterized by the production of regulator cells" refers to any condition wherein the number or activity of regulator cells plays a role in prolonging the disease state. Examples of such disease include, but are not limited to, cancer and infections.

As used herein the term "chronic persistent infection" refers to the presence of an infectious agent in the patient which is not readily controlled by the patient's immune system or available therapies. Examples include, but are not limited to, infections with HIV, the hepatitis B virus or the hepatitis C virus. To be classified as a "chronic persistent infection" it is preferred that the patient has at least had the infection for 3 months, more preferably at least 6 months.

As is known in the art, a cancer is generally considered as uncontrolled cell growth. The methods of the present invention can be used to treat any cancer including, but not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include breast cancer, prostate cancer, colon cancer, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, ovarian cancer, cervical cancer, gastrointestinal cancer, pancreatic cancer,

glioblastoma, liver cancer, bladder cancer, hepatoma, colorectal cancer, uterine cervical cancer, endometrial carcinoma, salivary gland carcinoma, mesothelioma, kidney cancer, vulval cancer, thyroid cancer, hepatic carcinoma, skin cancer, melanoma, brain cancer, neuroblastoma, myeloma, various types of head and neck cancer, acute lymphoblastic leukemia, acute myeloid leukemia, Ewing sarcoma and peripheral neuroepithelioma.

Unless otherwise indicated, the recombinant DNA and immunological techniques utilized in the present invention are standard procedures, well known to those skilled in the art. Such techniques are described and explained throughout the literature in sources such as, J. Perbal, A Practical Guide to Molecular Cloning, John Wiley and Sons (1984), J. Sambrook *et al*, Molecular Cloning: A Laboratory Manual, Cold Spring Harbour Laboratory Press (1989), T.A. Brown (editor), Essential Molecular Biology: A Practical Approach, Volumes 1 and 2, IRL Press (1991), D.M. Glover and B.D. Hames (editors), DNA Cloning: A Practical Approach, Volumes 1-4, IRL Press (1995 and 1996), and F.M. Ausubel *et al* (editors), Current Protocols in Molecular Biology, Greene Pub. Associates and Wiley-Interscience (1988, including all updates until present), Ed Harlow and David Lane (editors) Antibodies: A Laboratory Manual, Cold Spring Harbour Laboratory, (1988), and J.E. Coligan *et al* (editors) Current Protocols in Immunology, John Wiley & Sons (including all updates until present); and are incorporated herein by reference.

Acute Phase Inflammatory Markers

As mentioned above, some acute phase inflammatory markers initially increase during an immune response (referred to hereinafter as positive acute phase inflammatory markers) whilst others initially decrease during an immune response (referred to hereinafter as negative acute phase inflammatory markers). Acute phase inflammatory markers are also referred to in the art as acute phase reactants or acute phase proteins.

Examples of positive acute phase inflammatory markers include, but are not limited to, c-reactive protein, serum amyloid A, serum amyloid P component, complement proteins such C2, C3, C4, C5, C9, B, C1 inhibitor and C4 binding protein, fibrinogen, von Willebrand factor, α1-antitrypsin, α1-antichymotrypsin, α2-antiplasmin, heparin cofactor II, plasminogen activator inhibitor I, haptoglobin, haemopexin, ceruloplasmin, manganese superoxide dismutase, α1-acid glycoprotein, haeme oxygenase, mannose-binding protein, leukocyte protein I, lipoporotein (a) and lipopolysaccharide-binding protein.

Example of negative acute phase inflammatory markers include, but are not limited to, albumin, pre-albumin, transferin, apoAI, apoAII, α2 HS glycoprotein, inter-α-trypsin inhibitor, histidine-rich glycoprotein.

Serum amyloid A (SAA) was discovered as a plasma component that shares antigenicity with amyloid AA, the chief fibrillar component in reactive AA amyloid deposits. SAA has been shown to be an acute phase reactant whose level in blood is elevated to 1000-fold or higher as part of the body's responses to various injuries including trauma, infection and inflammation.

SAA levels can be determined as known in the art, see for example Weinstein *et al* (1984), Liuzzo *et al* (1994), O'Hara *et al* (2000), Kimura *et al* (2001) and O'Hanlon *et al* (2002).

C-reactive protein (CRP) is an important positive acute phase response protein, and its concentration in serum may increase as much as 1,000-fold during the acute phase response. CRP is a pentamer consisting of five identical subunits, each having a molecular weight of about 23,500.

C-reactive protein levels can be determined using techniques known in the art, these include, but are not limited to, those disclosed in Senju *et al* (1983), Weinstein *et al* (1984), Price *et al* (1987), Liuzzo *et al* (1994), Eda *et al* (1998), Kimura *et al* (2001) and O'Hanlon *et al* (2002).

Agents which Inhibit the Production of, Limit the Function of, and/or Destroy, Regulator Cells

The agent can be any factor or treatment which selectively or non-selectively results in the destruction, or the inhibition of the production, of regulator cells. For example, a CD4+ specific antibody could be used to specifically target CD4+ T cells. However, in some instances a non-selective agent could be used, such as an anti-proliferative drug or radiation, both of which destroy dividing cells. In particular, as with other cell types, regulator cells are particularly vulnerable to destruction by anti-mitotic (anti-proliferative) drugs or spindle poisons (e.g. Vinblastine or paclitaxel) when dividing and specifically in mitosis.

The term "anti-proliferative drug" is a term well understood in the art and refers to any compound that destroys dividing cells or inhibits them from undergoing further proliferation. Anti-proliferative drugs include, but are not limited to, mechlorethamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, hexamethyl-melamine, thiotepa, busulfan, carmustine, lomustine, semustine, streptozocin, dacarbazine, methotrexate, fluorouracil, floxuridine, cytarabine, mercaptopurine, thioguanine,

pentostatin, vinblastine, anhydro vinblastine, vincristine, etoposide, teniposide, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin, mitomycin, L-asparaginase, cisplatin, mitoxantrone, hydroxyurea, procarbazine, mitotane, aminoglutethimide, prednisone, hydroxyprogesterone caproate, medroprogesterone acetate, megestrol acetate, diethylstilbestrol, ethinyl estradiol, tamoxifen, testosterone propionate, radioactive isotopes, ricin A chain, taxol, diphtheria toxin, colchicine and pseudomonas exotoxin A.

The agents are usually administered in the dosage forms that are readily available to the skilled clinician, and are generally administered in their normally prescribed amounts (as for example, the amounts described in the Physician's Desk Reference, 55th Edition, 2001, or the amounts described in the manufacture's literature for the use of the agent).

In one embodiment, the agent is administered as a single bolus injection. In another embodiment, the agent is administered by infusion. The period of infusion can be, for example, at least 3 hours, at least 12 hours or at least 24 hours.

Recent studies have suggested that CD4+CD25+ T cells play an important role in regulating immune cells directed against self antigens (Salomon *et al*, 2000; Suri-Payer and Cantor, 2001). Furthermore, targeted ablation of CD4+CD25+ T cells has been shown to enhance the ability of an animal to control tumour growth (Onizuka *et al*, 1999; Shimizu *et al*, 1999; Sutmuller *et al*, 2001). Accordingly, CD4+CD25+ T cells could be acting as regulator cells as used herein. The activity of CD4+CD25+ T cells can be downregulated by anti-GITR, anti-CD28 and/or anti-CTLA-4 (Read *et al*, 2000; Takahashi *et al*, 2000; Shimizu *et al*, 2002). Thus, these antibodies may be useful as agents for use in the methods of the present invention.

Timing of Exposing the Subject to the Agent

For the investigator who randomly applies a single treatment of anti-proliferative chemotherapy to a cancer patient there is an approximate 1 in 14, to 1 in 15, chance of getting the timing right. A one in fourteen chance equates to a 7% probability of applying the therapy on the correct day, when the regulator cells are vulnerable to inactivation. If this is done, the tumour should regress mediated by immune destruction. More specifically, once the regulators cells have been removed by therapeutic intervention, the immune response against the tumour or virus can proceed unimpeded, ultimately leading to control of the disease.

As outlined above, the present invention relies on the phenomenon that the relative number of effector cells expands in response to an antigen before the regulator

cells. Accordingly, as used herein, the term "the activity of the effector cells is not significantly reduced" means that the timing of the administration of the agent is such that the agent exerts a proportionally greater effect against the regulator cells than the effector cells. It is clearly preferred that the agent is administered at a time when the ratio of effect against the regulator cells to the effect against effector cells is greatest.

In most instances, the time point that the agent is to be administered will need to be empirically determined in subjects at different stages of disease as their immune response kinetics may vary. Other factors such as the general health of the subject and/or the genetic makeup of the subject will also impact upon when is the appropriate time to administer the agent.

Techniques known in the art can be used to monitor the growing population of effector and/or regulator cells during the "cycle".

Serial blood samples can be collected and quantitatively screened for all CD4+ subsets by FACS analysis. This FACS monitoring will need to be maintained until the regulator cells begin clonally expanding in response to the disease state, whether produced by the tumour or administered to the subject. Other possible assays for monitoring the growing population of regulator cells include lymphocyte proliferation/activation assays and various cytokine level assays (for example an assay for IL-4, IL-6 or IL-10).

Also, serial blood samples can be collected and quantitatively screened for all effector cell activity such as but not limited to CD8+, CRP, SAA and various cytokines. Such effector cell markers will precede the regulator cell markers.

When the disease is cancer another avenue of determining the time point for administering the agent is to monitor the tumour load. It is envisaged that the tumour load decreases due to the activity of the effector cells, however, the subsequent increase in regulator cells would down-regulate the effector cells resulting in a slowing of the tumour load decrease. Accordingly, the agent could be administered approximately prior to the slowing of the decrease in tumour load. Techniques known in the art, for example RT-PCR or antibody detection, of markers expressed by the tumour, could be used to measure tumour load in these circumstances. Examples of suitable tumour antigen marker assays include, but are not limited to, for AFP (marker for hepatocellular carcinoma and germ-cell tumours), CA 15-3 (marker for numerous cancers including breast cancer), CA 19-9 (marker for numerous cancers including pancreatic cancer and biliary tract tumours), CA 125 (marker for various cancers including ovarian cancer), calcitonin (marker for various tumours including thyroid medullary carcinoma), catecholamines and metabolites (phaeochromoctoma), CEA

(marker for various cancers including colorectal cancers and other gastrointestinal cancers), hCG/beta hCG (marker for various cancers including germ-cell tumours and choriocarcinomas), 5HIAA in urine (carcinoid syndrome), PSA (prostate cancer), sertonin (carcinoid syndrome) and thyroglobulin (thyroid carcinoma).

Monitoring may need to be very frequent, for example as often as every few hours, to ensure the correct time point is selected for administration of the agent. Preferably, the monitoring is conducted at least every 48 hours. More preferably, the monitoring is conducted at least every 24 hours.

Optimally, the monitoring is continued to determine the affect of the agent. Insufficient ablation, re-emergence of the regulator cells or increases in, for example, tumour load will mean that the method of the present invention should be repeated. Such repeated cycles of treatment may generate immunological memory. It is therefore possible that the present invention, used in repetitive mode, may provide some prophylactic protective effect.

**EXAMPLES**

Example 1

An elderly female ovarian cancer patient was monitored for 12 days for fluctuations in the levels of c-reactive protein, serum amyloid A and the tumour marker CA125. Monitoring was performed using standard laboratory tests on blood samples collected every day. The patient had not recently been exposed to any anti-cancer therapy. Furthermore, there was no evidence that the patient was suffering from any diseases other than cancer. The CA125 (an ovarian cancer marker) was monitored as an indicator of disease burden.

As shown in Figure 1A, c-reactive protein (CRP) levels peaked at the beginning of the monitoring period. Furthermore, as shown in Figure 1B serum amyloid A levels were elevated at the same time of the CRP peak.

These results indicate that;

i) the levels of acute phase inflammatory proteins are fluctuating in a cancer patient in the absence of any other known factors which might cause these fluctuations such as viral infection or chemotherapy,

ii) elevated levels of acute phase inflammatory proteins was associated with lower levels of tumour antigens suggesting the presence of effector cells, and

iii) increased levels of tumour antigen is associated with lower levels of acute phase inflammatory proteins suggesting that regulator cells have counteracted the

beneficial activity of the effector cells such that these cells are no longer active against the tumour cells.

Example 2

A human subject suffering from a HIV infection was subjected to highly active antiretroviral therapy (HAART) for at least 6 months and then taken off the treatment. C-reactive protein levels were determined using standard techniques on samples obtained during and after the completion of HAART.

As can be seen in Figure 2, the results show that upon conclusion of HAART c-reactive protein levels began to cycle, peaking approximately every 14 days.

Example 3

Serum CRP was used to monitor the immune response in HIV patient who had stopped their anti-retroviral therapy (Figure 3). In this study CRP levels mimicked viral load fluctuations as the immune response switched on and off (Figure 3). It is interesting to note that these CRP fluctuations have an approximate 14 day cycle.

Example 4

The "Pubmed" database (http://www.ncbi.nlm.nih.gov/) was searched for the abstracts of journal articles which described the results of Phase II or Phase III clinical trials using anti-proliferative agents (such as vinblastine and taxol) for the treatment of cancer. Other criteria that were used to select the "abstracts" were that the cancer was at a late stage (stage III or stage IV) and the disease had disseminated. Some studies used a single drug whereas others used combinations. No other criteria were used and studies with an atypical complete response rate were not disregarded.

The complete response rate (as indicated in the abstracts) for each trial was used to determine the average complete response rate of each type of cancer. The results are provided as Table 1. Notably, the average complete response rate varied only a small degree, namely between 5.1 to 8.2% for all cancers analysed. The results provided in Table 1 were used to determine the overall average complete response rate. This average complete response rate was 6.6% over at least 10 different types of cancers when considering the 144 trials analysed.

With specific regard to the data provided for ovarian cancer it should be noted that one study (Adachi et al., 2001) observed a complete response rate of 25% which was very large compared to the other 143 trials. This study looked at eight patients, with two patients providing a complete response rate. Whilst this is well within the

realms of possibility, if the study is ignored the overall complete response rate for the remaining ovarian cancer studies is 7.1%.

The complete response rates are remarkably consistent between the different cancers, and treatment regimes thereof, suggesting an underlying factor relevant to all cancers and anti-proliferative treatments. As described herein, this factor is that effector cells and regulator cells are cycling. Accordingly, it can be argued that the complete response rates provided in Table 1 are the result of the anti-proliferative agent being administered at an appropriate time such that effector cell numbers are maximized whilst regulator cell numbers are reduced or removed, or activity is down-regulated or compromised, by the anti-proliferative agent sufficient to elicit a complete response.

*Table 1 - Complete Response Rates Resulting from Clinical Trails with Anti-Proliferative Drugs against Various Cancers.*

| Cancer Type | Complete Response Rate (%) | Number of Trials |
|---|---|---|
| Mesothelioma[a] | 5.1 | 10 |
| Gastric[b] | 7.33 | 15 |
| Hepatocellular[c] | 6.6 | 8 |
| Pancreatic[d] | 7.35 | 4 |
| Melanoma[e] | 7.5 | 15 |
| Prostate[f] | 5.15 | 7 |
| NSC Lung[g] | 5.85 | 6 |
| Breast[h] | 7.36 | 19 |
| Ovarian[i] | 8.2 | 15 |
| Colorectal[j] | 6.85 | 28 |
| Miscellaneous[k] | 6.0 | 17 |

[a] Tsavaris *et al* (1997), Monnet *et al* (2002), Pinto *et al* (2001), Kindler *et al* (1999), Yogelzang *et al* (1997), Planting *et al* (1995), Chahinian *et al* (1993), Raghavan *et al* (1990), Henss *et al* (1988) and Mbidde *et al* (1986).

[b] Kollmannsberger *et al* (2000), Sugimachi *et al* (2000), Jeen *et al* (2001), Yamada *et al* (2001), Aitini *et al* (2001), Cho *et al* (2002), Kornek *et al* (2002), Hofheinz *et al* (2002), Constenla *et al* (2002), Kim *et al* (2002), Louvet *et al* (2002), Kikuyama *et al* (2002), Bar Sela *et al* (2002), Murad *et al* (1999) and Sakata *et al* (1998).

[c] Porta *et al* (1995), Pohl *et al* (2001), Oon *et al* (1980), Choi *et al* (1984), Zeng *et al* (1998), Carr *et al* (1997), Patt *et al* (2003) and Leung *et al* (1999).

[d] Murad *et al* (2003), Ashamalla *et al* (2003), Safran *et al* (2002) and Sherman *et al* (2001).

[e] Retsas *et al* (1996), Nathan *et al* (2000), Bafaloukos *et al* (2002), Bafaloukos *et al* (2002), Buzaid *et al* (1998), Gibbs *et al* (2000), Atkins *et al* (2002), Gundersen *et al*

(1989), Johnson *et al* (1985), Nystrom *et al* (2003), Einzig *et al* (1991), Bedikian *et al* (1995), Einzig *et al* (1996), Nathan *et al* (2000) and Chapman *et al* (2002).

[f] Hudes *et al* (1997), Kelly *et al* (2001), Savarese *et al* (1999), Small *et al* (2001), Savarese *et al* (2001), Trivedi *et al* (2000) and Picus *et al* (1999).

[g] Mariotta *et al* (2002), Recchia *et al* (2002), Perng *et al* (2000), Ginopoulos *et al* (1999), Paccagnella *et al* (1996) and Agelaki *et al* (2001).

[h] Freyer *et al* (2003), Morabito *et al* (2003), Kosmas *et al* (2003), Gebbia *et al* (2003), Thomas *et al* (1994), Romero *et al* (1994), Pectasides *et al* (2001), Frasci *et al* (2002), Stathopoulos *et al* (2002), Gomez-Bernal *et al* (2003), Freyer *et al* (2003), Kornek *et al* (1998), Michelotti *et al* (1996), Kakolyris *et al* (1999), Twelves *et al* (1994), Fumoleau *et al* (1993) and Ibrahim *et al* (1999).

[i] Li *et al* (2002), Sehouli *et al* (2002), Rose *et al* (2003), Faivre *et al* (2002), Dieras *et al* (2002), Adachi *et al* (2001), Sutton *et al* (1994), McClay *et al* (1995), Manetta *et al* (1994), Guastalla *et al* (1994), Covens *et al* (1992), Einzig AI. (1994), Kjorstad *et al* (1992), Ozols *et al* (1984), Planner *et al* (1996) and Amadori *et al* (1997).

[j] Cassinello *et al* (2003), Glimelius *et al* (2002), Calvo *et al* (2002), Scheithauer *et al* (2002), Neri *et al* (2002), Falcone *et al* (2001), Kouroussis *et al* (2001), Meropol *et al* (2001), Comella *et al* (2000), Cascinu *et al* (1999), Sobrero *et al* (1995), Gamelin *et al* (1998), Romero *et al* (1998), Beerblock *et al* (1997), Blanke *et al* (1997), Grem *et al* (1993), Jeremic *et al* (1993), Posner *et al* (1992), Sinnige *et al* (1990), LoRusso *et al* (1989), Petrelli *et al* (1989), Valdivieso *et al* (1981), Cassinello *et al* (2003), Reina *et al* (2003), Comella *et al* (1999), Neri *et al* (1998), Pyrhonen *et al* (1992) and Beck *et al* (1984).

[k] Cancers included renal cell carcinoma, adenocarcinoma, squamous cell carcinoma, uterine cervical cancer, glioblastoma multiforme, metastatic osteosarcoma, urothelial cancer and endometrial cancer. Described by Schornagel *et al* (1989), Liu *et al* (2001), Forastiere *et al* (1987), Okuno *et al* (2002), Takasugi *et al* (1984), Hurteloup *et al* (1986), Kakolyris *et al* (2002), Morris *et al* (1998), Takeuchi *et al* (1991), Fountzilas *et al* (1999), Rosenthal *et al* (2000), Goorin *et al* (2002), Rodriguez-Galindo *et al* (2002), Ahmad *et al* (2002), DiPaola *et al* (2003) and Lissoni *et al* (1996).

If the typical cycle of effector/regulator cell numbers is considered as 15 days, the data in Table 1 suggest a one day window to administer the anti-cancer therapy to achieve a complete response rate. Partial response rates in the order of 30% are typically noted suggesting that if the agent is administered at a 24 to 36 hour period either side of this "one day window" a beneficial effect can also be achieved.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

All publications discussed above are incorporated herein in their entirety.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Dated this twenty-fourth day of October 2003

ImmunAid Pty Ltd
Patent Attorneys for the Applicant:

F B RICE & CO

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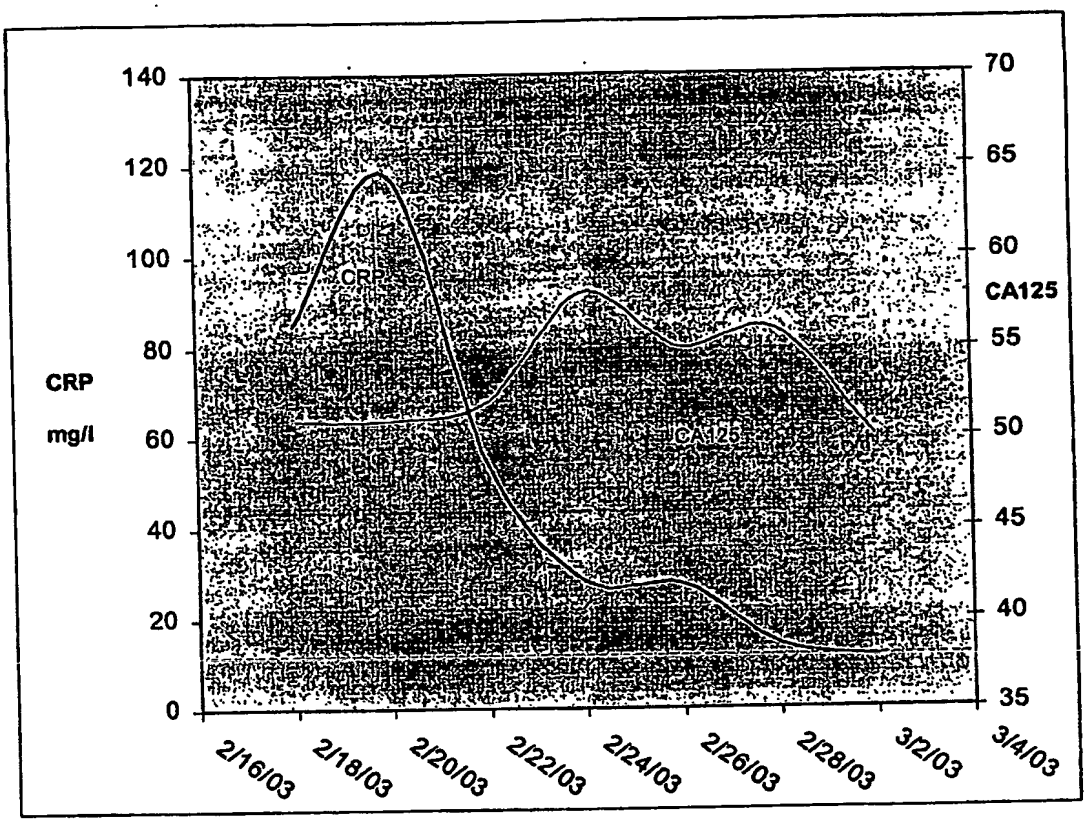


Figure 1A

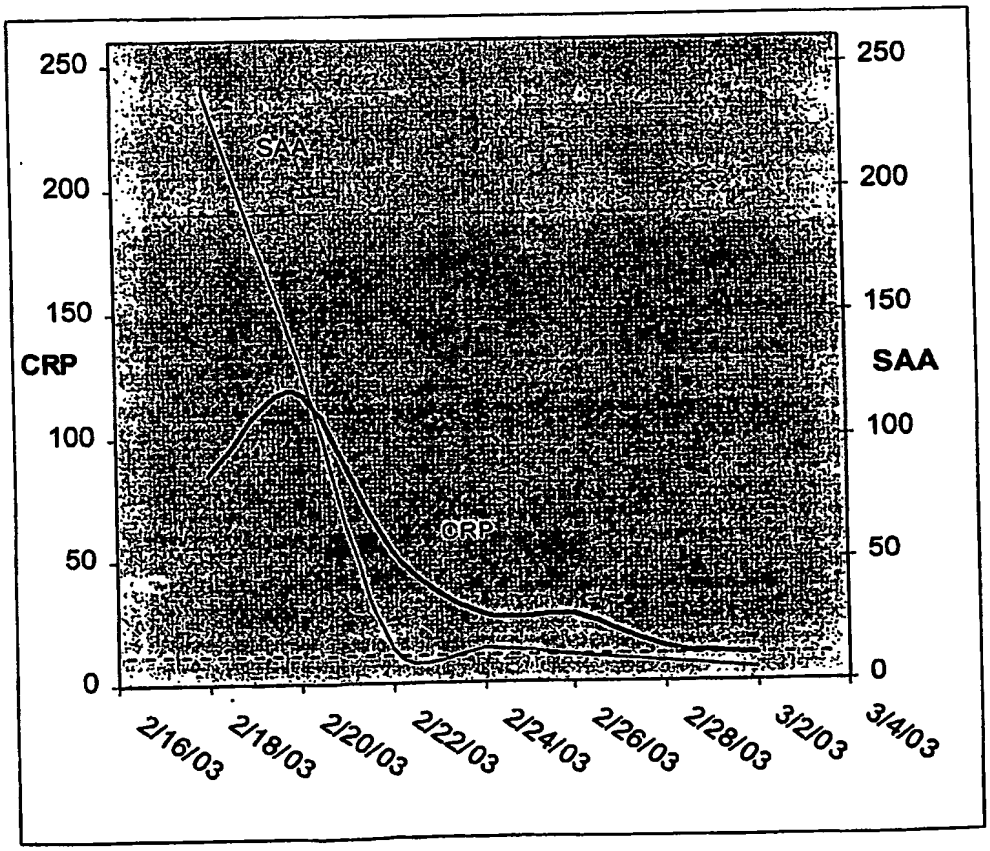


Figure 1B

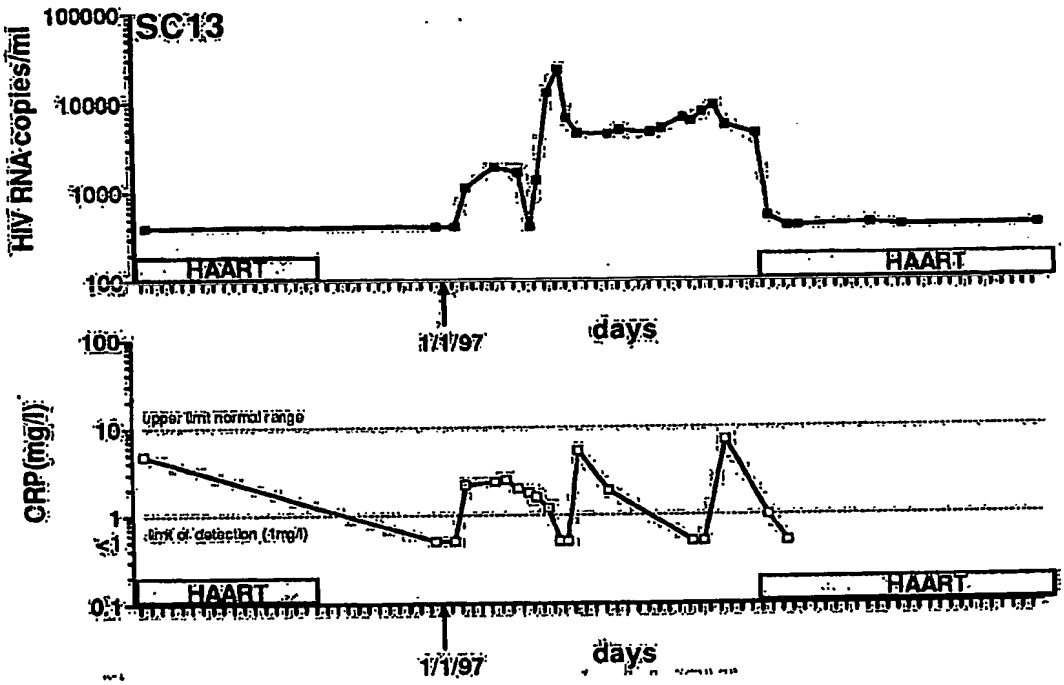
SC13
HIV RNA copies/ml
100000
10000
1000
100
HAART
HAART
1/1/97
days
CRP (mg/l)
100
10
1
0.1
upper limit normal range
limit of detection (1mg/l)
HAART
HAART
1/1/97
days

Figure 2

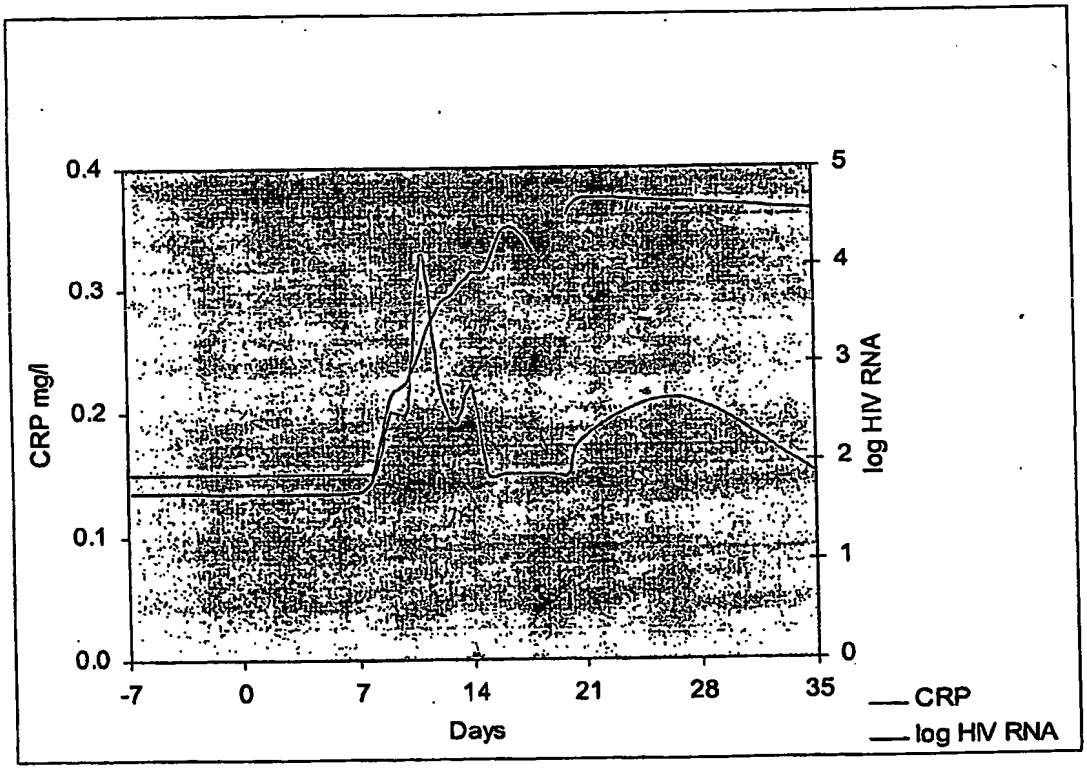
0.4
0.3
0.2
0.1
0.0
CRP mg/l
5
4
3
2
1
0
log HIV RNA
-7
0
7
14
21
28
35
Days
CRP
log HIV RNA

Figure 3

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